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# The Relationship between *Helicobacter pylori* Infection and Atherosclerosis: A Meta-analysis

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Review

ABSTRACT

**Objective:** Both humoral and cellular immune responses are affected in atherosclerosis. Therefore, some investigators have focused on infectious causes and inflammatory processes involved in the development of atherosclerosis. This systematic review and meta-analysis was designed to investigate the relationship between *Helicobacter pylori* infection and atherosclerosis.

**Materials and Methods:** The current review was conducted on studies published from January 1, 2000 to November 15, 2014 through Scopus, Web of sciences, Google scholar, Embase, and two MEDLINE database engines: PubMed and Ovid. Different combinations of the following keywords "*Helicobacter pylori*, *H. pylori*, atherosclerotic plaques, atherosclerotic lesion, and atherosclerotic vascular disease" were used.

**Results:** Four good-quality investigations met our inclusion criteria. The pooled odd ratio (OR) for the presence of *H. pylori* in the atherosclerotic plaques of patients with atherosclerotic vascular disease in a fixed model was 4.65 (95% CI = 1.99–10.85,  $p=0.001$ ). According to the chi-square test, there was a significant heterogeneity (67.6%) among studies ( $p=0.026$ ). In a random effects method, the pooled OR was 5.98 (95% CI=0.69–51.99,  $p=0.10$ ).

**Conclusion:** According to the results of this meta-analysis, *H. pylori* is not a significant risk factor for atherosclerotic vascular disease. However, evidence on this effect is inadequate. Hence, more original studies are still needed.

**Keywords:** Atherosclerosis, *Helicobacter pylori*, inflammation, infection, disease eradication

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## INTRODUCTION

Atherosclerosis is a major cause of mortality and morbidity in industrialized countries. It is a multifactorial disorder. Factors such as hypertension, smoking, hypercholesterolemia, and diabetes mellitus are widely accepted as atherogenic risk factors (1-3). Both humoral and cellular immune responses are affected in atherosclerosis (2, 4-6). Therefore, a heterogeneous aggregation of inflammatory cells, such as T-lymphocytes and activated macrophages, can be found in atherosclerotic plaques (7). Macrophages might be attracted in the atherosclerotic lesions and intimal layer of the artery by infectious agents (8). Although the mechanisms of the activation of inflammatory cells within atherosclerotic lesions are not fully explained (9, 10), histopathologic findings suggest the role of infectious agents and inflammatory processes in the pathogenesis of atherosclerosis (3, 11). Therefore, some investigators have focused on the infectious causes and inflammatory processes involved in the development of atherosclerosis (12). Recently, several studies have described the association of *Helicobacter Pylori* (*H. pylori*) with extra gastric diseases, such as ischemic heart diseases, as the most common clinical manifestation of atherosclerosis (13, 14). A number of sero-epidemiological studies (15) have focused on the relationship between the serologic evidence of *H. pylori* and atherosclerosis, and some of them found *H. pylori* DNA in atherosclerotic plaques (10, 16). Usually, samples obtained from the internal mammary artery—as a main source for grafting coronary artery—were studied; however, some investigators used the carotid body to detect the evidence of infection in atherosclerotic plaques (17). The present systematic review and meta-analysis was designed to investigate the relationship between *H. pylori* infection and atherosclerosis.

## MATERIALS and METHODS

### Search strategy

The current review was conducted on studies published since January 1, 2000, to November 15, 2014. An electronic literature search was carried out on Scopus, Web of sciences, Google scholar, Embase, and two MEDLINE databases: PubMed and Ovid, using different combinations of the following key words "*Helicobacter pylori*, *H. pylori*, atherosclerotic plaques, atherosclerotic lesion, atherosclerotic vascular disease." The Iranian databases, such as MagIran, IranMedex, and SID, were also searched with relevant English and Persian key words. The

search sensitivity was checked by considering duplicated papers. If the full text of articles were not accessible, emails were sent to the authors and full texts of the concerned papers were requested. We excluded the abstracts if the authors did not respond after one month of our first email and if the abstract was non-informative.

### Study selection

Published studies in all languages were eligible if they met the following criteria: a) Languages: English, French, and Persian full texts or an informative abstract in English; b) Appropriate study design: case-control, clinical trial, and cohort; c) Report of *H. pylori* prevalence in patients with atherosclerotic vascular disease; d) detecting of *H. pylori* through PCR DNA.

### Quality assessment

A critical appraisal (CA) was performed using the Epible check list form (18) to evaluate the adequacy of the sample size, design, data collection, and the resultant presentation. Each paper was appraised by two authors individually. Then, the two CA scores of each paper were compared together. If the difference was more than 10 percent, authors negotiated to reach the same CA score. Based on the total CA score, articles were classified as low (<40%), moderate (40–70%), and high (>70%) quality. Low quality papers were not included in the main analysis except in subgroups analysis, according to the papers' quality.

### Statistical analysis

The odds ratio (OR) with 95% confidence intervals (CIs) was calculated in each study by using data regarding the prevalence of *H. pylori* DNA in patients with and without atherosclerotic vascular disease. Chi-square tests were used for the assessment of heterogeneity or homogeneity between studies. A p value less than 0.1 was considered as significant heterogeneity. Regarding our low sample size, in the first step, we used the fixed Mantel–Haenszel model to achieve the pooled OR. However, according to the chi-square test and the presence of heterogeneity between studies, the random effects Mantel–Haenszel model was used to achieve pooled OR. The Begg–Mazumdar test was also used to assess the publication bias, and a p value <0.05 represented a significant publication bias.

## RESULTS

### Search results

Via database searching according our keywords, we obtained 1034 papers. Sixty two papers were excluded due to duplicate publication. A total of 917 manuscripts were also removed after checking the titles because they were not related or were not original research. Next, in the abstract evaluation of 55 papers, 48

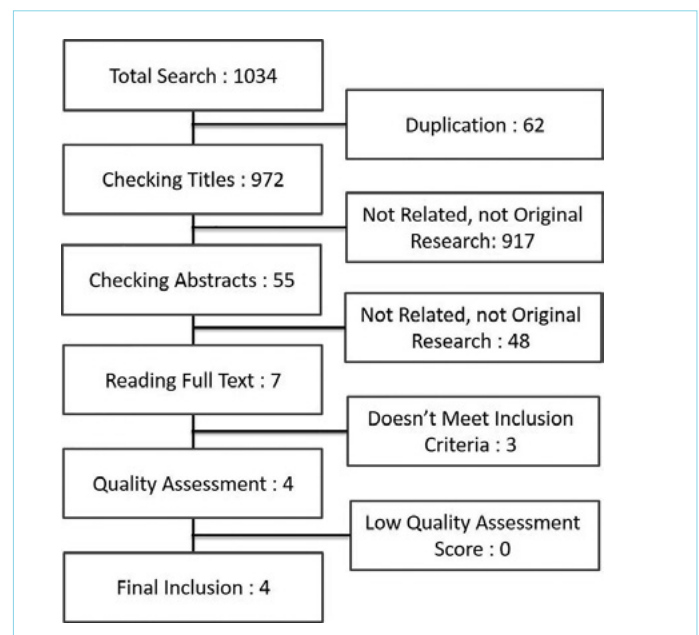
manuscripts were excluded and we read the full text of seven papers. In this step, we excluded three articles which did not have a control group and just reported the prevalence of *H. pylori* DNA detection in patients with atherosclerosis (19-21). Finally, four high quality investigations remained that met our inclusion criteria (21-24). Figure 1 shows the PRISMA flowchart.

### Characteristics of the studies

Finally four investigations from four countries (i.e., Turkey, Germany, Argentina, and Poland) were included in this study. These studies assessed the prevalence of *H. pylori* in patients with atherosclerotic vascular disease. In total, 75% of the studies were from Europe and 25% from the south of America. All of the enrolled studies were case-controlled and all of them used PCR DNA as the diagnostic method for detecting *H. pylori*. The characteristics of the mentioned studies are presented in Table 1. Table 2 shows data on the prevalence of *H. pylori* in patients with and without Atherosclerotic Vascular Diseases (22-25).

### Meta-analysis for the prevalence of *H. pylori* and atherosclerotic vascular diseases–*H. pylori* coexistence

Pooled OR for the presence of *H. pylori* in the atherosclerotic plaques of patients with atherosclerotic vascular diseases in a fixed



**Figure 1.** Screening of studies according to the PRISMA statement

**Table 1.** Characteristics of the studies

Author	Year	Country	Method	Sample size (CAD or CVD)	Healthy control	Diagnostic method of HP
Iriz et al. (22)	2008	Turkey	Case-Control	42	10	PCR DNA
Kowalski et al. (23)	2002	Germany	Case-Control	46	19	PCR DNA
Ameriso et al. (24)	2001	Argentina	Case-Control	38	7	PCR DNA
Reszka et al. (25)	2007	Poland	Case-Control	40	20	PCR DNA

CAD: coronary artery disease; CVD: cerebrovascular disease; HP: *Helicobacter pylori*; QAS: Quality Assessment Score

**Table 2.** Prevalence of HP and atherosclerotic vascular disease - HP coexistence in the studies

Author	Atherosclerotic Vascular Disease (CAD or CVD)		Control		OR (95% CI)
	HP (+)	HP (-)	HP (+)	HP (-)	
Iriz et al. (22)	11	31	0	10	7.67 (0.42–141.62)
Kowalski et al. (23)	22	24	0	19	35.82 (2.04–628.46)
Ameriso et al. (24)	20	18	0	7	16.62 (0.89–311.58)
Reszka et al. (25)	32	8	17	3	0.71 (0.17–3.01)

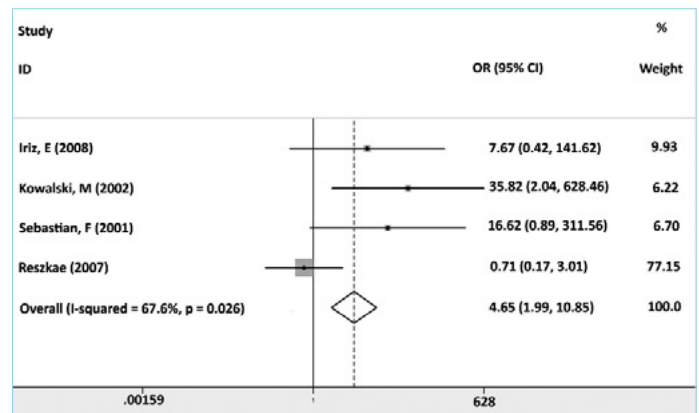
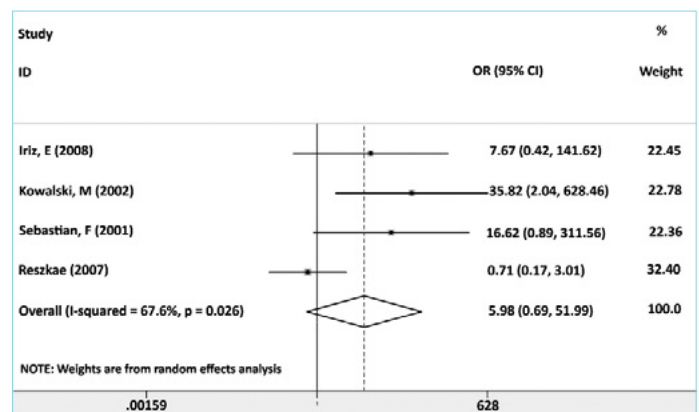
CAD: Coronary Artery Disease; CVD: Cerebrovascular Disease; HP: *Helicobacter pylori*

model was 4.65 with a 95% CI of 1.99–10.85 and  $p=0.001$  (Figure 2). However, according to the chi-square tests, there was a significant heterogeneity (67.6%) between studies ( $p=0.026$ ). Consequently, we conducted meta-regression analysis to find the source of this heterogeneity. The mean age of the case group was the only factor that had been reported among all studies but it was not a source of heterogeneity ( $p=0.12$ ). Therefore, in a random effects method, the pooled OR was 5.98 with a 95% CI of 0.69–51.99 and  $p=0.10$  ( $I^2=67.6\%$ ,  $p=0.026$ , N comparisons=4) (Figure 3). Through Egger's test, we did not find a significant publication bias (Table 3).

## DISCUSSION

For the first time, in this meta-analysis, we evaluated four case-control studies which investigated the presence of *H. pylori* DNA in patients with atherosclerotic vascular disease through PCR methods. We obtained a significant OR based on a fixed model for this association. However, due to heterogeneity, the OR related to the relationship between *H. pylori* infection and atherosclerosis was not significant based on the random effects model. Unfortunately, we could not get data regarding the lipid profile, leukocyte count, C-reactive protein, and other related variables from the included studies to.

As we pointed out before, atherosclerosis, as an important underlying causes for cardiovascular and cerebrovascular diseases, cannot be fully explained by traditional risk factors like smoking, hypertension, and dyslipidemia (26, 27), and now atherosclerosis is known as a chronic inflammatory disease of the arteries (28). There are some viruses and bacteria (i.e., cytomegalovirus and chlamydia pneumonia) that are considered to have a relationship with atherosclerosis (10, 28-31). Now, the literature has some powerful evidence about this association, especially about cytomegalovirus (10, 31). In 1994, Mendall et al. (32) showed that patients with coronary heart disease have elevated levels of serum antibodies related to *H. pylori*. Following this pioneer finding, some other studies proposed an relationship between atherosclerosis and coronary artery diseases with *H. pylori* infection (2, 27). *H. pylori* as a gram-negative bacterium naturally colonizes the epithelium of the human stomach. However, there is some evidence that proposes some extra gastric manifestations for this microorganism, such as idiopathic thrombocytopenic purpura and the initiation or development of atherosclerosis (25, 32).

**Figure 2.** Relationship between *H. pylori* and atherosclerosis in a fixed effects model**Figure 3.** Relationship between *H. pylori* and atherosclerosis in random effects models**Table 3.** Publication bias checked by the Begg's test

Variables	Values
Kendall's score (P-Q)	2
Std. deviation of score	2.94
p	0.68

CAD: Coronary Artery Disease; CVD: Cerebrovascular Disease; HP: *Helicobacter pylori*

Consistent with the theory of the effect of *H. pylori* infection on the development of atherosclerosis, recently a decline in the epidemics of duodenal ulcers and coronary atherosclerosis was reported (33). Furthermore, it was shown that the mean values of carotid artery intima-media thickness, as a marker of clinical and subclinical atherosclerosis, (34) are higher in patients with *H. pylori* infection, especially in those infected with the cytotoxin-associated gene A (Cag A) positive strain (35). In contrast with this theory, Jia al. (36), in a cross-sectional study on 961 patients who had undergone coronary angiography, could not find a significant relationship between coronary atherosclerosis and *H. pylori* infection. However, they found a good correlation between this infection and a decrease in the high-density lipoprotein (HDL) cholesterol. Perhaps, changing the lipid profile and inducing a dyslipidemia status might be a mechanism for the development of atherosclerosis after *H. pylori* infection (36). Consistent with this hypothesis, some of the studies have reported that *H. pylori* infection can lead to a decrease in HDL (37) and an increase in the triglyceride concentrations (38). Also, it was proposed that the eradication of *H. pylori* can lead to a significant decrease in total cholesterol concentration (38). Data about cerebrovascular diseases as another manifestation of atherosclerosis are controversial. A meta-analysis in 2012 showed that there is a close relationship between chronic *H. pylori* infections and ischemic stroke (39). However, another meta-analysis in 2014 could not find a powerful relationship between *H. pylori* infection and stroke, even in those infected with the Cag A positive strains (40).

There are some proposed mechanisms for the role of *H. pylori* infection in the development of atherosclerosis. Endothelial dysfunction is one of them and is attributed to vacA and also to the nutritional effect of this microorganism, which usually results in the malabsorption of folate and the vitamins B6 and B<sub>12</sub> and also hyperhomocysteinemia, which is toxic to endothelial cells (41, 42).

Additionally, it has been shown that endothelial dysfunction improves after the eradication of *H. pylori* infection (3). It should be noted that some evidence does not support the linkage between *H. pylori* infection and endothelial dysfunction (44, 45). *H. pylori* as an infection can lead to at least a low grade persistent systemic inflammation and stimulates the production of some inflammatory cytokines, such as Il-6, CRP, and Il-18. These cytokines can influence the process of atherosclerosis (46-48). Molecular mimicry between Cag A (an antigen related to *H. pylori*) and proteins presented in the wall of medium and large-sized arteries is another proposed mechanism for the initiation and development of atherosclerosis by *H. pylori* infection. It is reported that anti Cag A antibodies can react with both Cag A and vascular antigens, such that it can be effective in the pathogenesis of atherosclerosis (49, 50). However, a recently published meta-analysis showed that there is no strong relationship between Cag A positive infection and stroke (40). There are also some other theories about the effects of *H. pylori* on the development of atherosclerosis, such as oxidative stress, modifying the lipid profile, and platelet aggregation (1).

#### Limitation

In this meta-analysis, we only found four studies that matched our inclusion criteria. These studies had small sample sizes and also prepared the samples of atherosclerotic plaques from a different vessel, which might affect the results of the present study.

#### Recommendation

We suggest more original studies about this issue with larger sample sizes, while utilizing the same method for detecting *H. pylori* infection and the samples of the same vessels. A more powerful meta-analysis with definite results can then be conducted.

#### CONCLUSION

According to the results of this meta-analysis, *H. pylori* is not a significant risk factor for atherosclerotic vascular disease. However, evidence on this effect is inadequate. Hence, more original studies are still needed.

**Peer-review:** Externally peer-reviewed.

**Authors' Contributions:** Idea development: MRB, BP. Searching databases: AS, MSRZ. Title, abstract, and fulltext screening: MRB, AMJ, MS, AS, MSRZ, HKS, BP. Data analysis: MSi. Writing the manuscript: all of the authors. All authors have read and approved the final manuscript.

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